THE CURE OF TUBERCULOSIS BY OXYTUBERCULINE, WITH EXPERIMENTS ON PATIENTS, ANIMALS AND CULTURES.

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In the November number of the *Occidental Medical Times* of last year I described a method of treatment of tuberculosis that was based upon some original conceptions of the mode of generation of antitoxines in the animal body. Further research and clinical experience have enabled me to confirm the statements made at the time, and also those in an additional note published one month later. My clinical observations and those of my colleagues who have investigated the remedy, place the efficacy of oxytuberculine beyond doubt. Culture experiments, as you will see, show how the agent acts and enable us to measure the potency of each preparation of the oxytuberculine in a manner that has not yet been possible with any of the antitoxic serums.

Before the year 1890 the attitude of the medical profession towards tuberculosis was that of absolute helplessness. We had learned to diagnosticate the disease in its early stages by the microscopic examination of the sputum through the presence of the bacillus tuberculosis, but we felt that when we had discovered the dreaded disease, all that we could do was to send the hapless patient to a congenial climate in the hope that fresh air and exercise might benefit. As far as active therapeutic intervention was concerned, however, we knew that we could do nothing. Then came the glad tidings that Koch had found the long sought for specific; that his tuberculine was the certain cure for tuberculosis, wherever it might be found. We shall probably never again witness such an enthusiasm in medical circles as that which was aroused by Koch's demonstration. We had learned to look upon his statements as demonstrated facts, for he had never, until then, enunciated a doctrine that had not been found to be correct.

We even felt that the secrecy of the remedy was to be forgiven in him—although in another such a procedure would have been considered quackish. Truly, it seemed marvelous that an infinitesimal quantity of an organic liquid injected under the skin of a tubercular individual should cause a violent febrile reaction, with congestion of the tubercular mass and no effect on other tissues. Every one was eager to try the new remedy, even if he did not know what it was, and happy was he if he were one of the favored few who could obtain it at any price.

But the reaction came only too soon. The great Virchow showed at the post-mortem table what was really the influence of the tuberculine. In a large number of cases death was hastened by its use, and dissemination of tubercle was induced by it, such as the great pathologist had not seen before. From that time on the credit of tuberculine began to wane, and soon it fell into disrepute with the vast majority of physicians, as a remedy for tuberculosis. It still holds its place for diagnostic purposes, for the febrile reaction following its injection is a certain sign that tuberculosis is somewhere present in the body.

We now know what tuberculine is and how it is prepared. Upon the surface of veal boullion containing glycerine and peptone a pure culture of the bacillus tuberculosis is floated and cultivated at 38 degrees C. After six to eight weeks a pellicle will have covered the surface and sunk to the bottom of the vessel. The fluid is then sterilized by heat, filtered through a Pasteur filter and evaporated to one-tenth its volume. This is the crude tuberculine such as was formerly used. Now this crude liquid is precipitated with alcohol, washed and dissolved in water.

Feeling that there was an element of truth in the statements of Koch that tuberculine cures consumption, and that the ill-effects resulting from its use must be due to some extraneous foreign elements that were the deleterious agents, several have attempted to purify it and have used what they supposed to be a purified tuberculine under various names. The most prominent of these preparations is that of Klebs, which he terms antiphthisine. Unfortunately, the claims made by Klebs have not been confirmed by experience. Tru-

deau has clearly proved that antiphthisine is merely a very dilute tuberculine. We shall see during the course of these remarks that Trudeau was quite correct when he stated that Klebs erred in affirming that tuberculine inhibited the growth of the tuberculosis bacillus. Trudeau showed that it is the acid which develops in the culture fluid that acts as a preventive of further growth.

I can confirm Trudeau's statements, for in equal parts of tuberculine and veal boullion that has been made alkaline, the tuberculosis bacillus grows as luxuriantly as in the plain veal boullion. Clinical observations have been as adverse to the claims of Klebs as have been laboratory experiments.

In 1890 Behring enunciated the doctrine of the antitoxine substances which develop in the animal organism from the bacterial toxines and led to the introduction of the antitoxine of diphtheria into general medical practice. In spite of occasional adverse criticism and occasional death due directly to the remedy, it has proved its value in the treatment of diphtheria beyond a doubt and thousands of lives are yearly saved that would otherwise undoubtedly have been lost.

Stimulated by these excellent results numerous investigators have attacked tuberculosis in a similar manner, and have probably obtained some good results. This is true of Paquin, in our country, and Maragliano, in Italy. Their method of procedure is to inject gradually increasing quantities of tuberculine hypodermically into a horse until the animal becomes immune to such large injections. The blood is drawn from the jugular vein into a sterile flask, allowed to coagulate in a cool place and the sterile serum drawn off for use as the antitoxine. It will require a long observation of results by many clinicians before we will be able to arrive at a knowledge of just how much may be accomplished by this serum. But even if it should be finally proved that an antituberculine develops in animals so treated, its use as a curative agent in man is attended with several obstacles and dangers. In the first place, the quantity of tuberculine used, and hence the quantity of antituberculine developed, is so infinitesimal that when dissolved in the blood and plasma of the animal, it is present in such minute proportions that the numeral would be far removed from the decimal point in its repre-

sentation in figures. In the second place the antituberculine elaborated in the blood must be administered dissolved in the serum of the animal. We know from several deaths that have immediately followed the administration of the diphtheria antoxine, that this is by no means an indifferent substance which may be administered in unlimited quantities. The antitoxine we know develops in the animal body in some manner from the toxine. If we were able to discover by what process the body evolves the antitoxine from the toxine, it is clear that we might be able in our laboratories to imitate the method, and so produce the sought for remedy in unlimited quantities and free from deleterious admixture. Until now no satisfactory theory has been established, and no indication had been given of the lines upon which to proceed.

With regard to tuberculosis, however, it seems to me that the course to pursue has long been before the medical profession, even though we were unable to read what nature had written for us in her hieroglyphics.

The theory which lies at the foundation of the therapeutic measures about to be described, is even more important than the results themselves, for, if it should be found correct, it will be an addition to our biological knowledge of the greatest scientific importance. This theory was thought out early in October, 1895, and the various modes in which it might be practically applied were clear before a single step was taken. In other words, the theory was not evolved from the therapeutic results, but the method of treatment was a consequence of the biological proposition. The therapeutic success may therefore be looked upon as a verified prediction, and hence has far greater evidential value than it otherwise could have. The treatment of patients by the new method was very cautiously begun on October 22d, 1895, and, as the results warranted, the doses were gradually increased until after a few months efficient quantities were administered. I am pleased to be able to say that to my knowledge no patient has been injured by its use.

In 1864, Spencer Wells performed laparotomy, in consequence of an erroneous diagnosis, upon a case of tubercular peritonitis. Contrary to all expectations the patient recovered. Numerous cases have been since reported in which the same favorable re-

sults occurred; indeed, the peritoneum that was seen at the operation to be studded with tubercles, has been found years after, at a second operation, to be smooth and free from all tubercular deposit. Distant tuberculosis has also been observed to disappear after such laparotomies upon tubercular peritoneums. It appears most probable that in these cases the entrance of air into the peritoneal cavity must have been the important factor; that an oxidation of the tuberculine present in the effusion was thus brought about, and that it was this oxytuberculine which effected the cure both of the local and of the general tuberculosis. It certainly seems a very probable hypothesis that it is oxidation whereby the toxine is changed into the antitoxine in the animal body, for there is no process of the economy so universal as oxidation. The first and most evident result of the introduction of a toxine is fever with increased oxidation, as if nature was striving with all her power to change by this process the poisonous substance into its antidote.

Acting upon this hypothesis it became the problem to find a method of oxidizing the toxine without completely destroying it, and various methods of accomplishing this result were investigated. I will not weary you with a description of the different forms of experiment that were attempted, nor of the steps that were taken until the method was finally perfected, but shall describe to you in as detailed a manner as I can the mode in which oxytuberculine is now manufactured. I found very soon, in the course of my experiments, that the peroxide of hydrogen is the substance for which I was seeking, that it was a powerful oxidizer but not so destructive as was generally supposed. When I added it to tuberculine, in the cold, and injected the latter into a tubercular patient or animal, even after the mixture had stood for some time, it produced the same reaction as if pure tuberculine had been used. I found that in order to avoid such reaction it was necessary to heat the mixture for at least ninety-six hours. I have lately found it wise to lengthen the period of heating even more, and now sterilize for 120 hours, obtaining better results that I did when the action was continued only 96 hours. I formerly used the tuberculine prepared by Koch in Berlin, but have been able to obtain still better results with one of my own growth made by the development of a highly virulent bacillus of tuberculosis upon

veal bouillon containing four per cent glycerine, one per cent peptone, and one-half per cent of chloride of sodium, to every liter of which when neutralized 3 c.c. of a normal solution of carbonate of sodium is added. In this culture fluid the germ has developed with gradually increasing rapidity so that, whereas, ordinarily it takes six weeks for the culture fluid to be completely covered with the growth, this now occurs with our germ in less than three weeks. Injected into guinea pigs it kills many of them in less than three weeks, the organs being overwhelmed with tubercular nodules, as you can see from this specimen.

After the germ has fully grown so that the tubercular scum that floats on the surface begins to sink, the flask is sterilized by heat for two hours and the contents filtered. This is the tuberculine I use. A measured quantity is put into a stone jug and one-tenth the quantity of a ten volume solution of the peroxide of hydrogen is added, the jug stoppered with cotton and put into a sterilizer at 100° C. Every twelve hours the same quantity of the same peroxide of hydrogen is added until the process shall have been repeated the tenth time, so that in all the quantity of solution of peroxide of hydrogen added shall equal the quantity of tuberculine used. This is then heated to 100° C. for twelve hours longer, and at the end of that time (120 hours in all) it is still found to contain free peroxide of hydrogen, is highly acid and decidedly darker than was the original tuberculine. It is made alkaline with caustic soda and reheated to drive off the excess of peroxide of hydrogen; 5 per cent of boric acid is added to keep it from decomposing. It is filtered into sterile vessels and is ready for use. It now does not contain a trace of the peroxide of hydrogen which has all been changed to water.

Theoretical objections have been made to the process by some who claim that the peroxide of hydrogen must be rapidly destroyed by the organic substances present in the liquid. It is very easy to prove that this supposition is incorrect, for at any stage of the process up to the final addition of the alkali, free peroxide of hydrogen may be found by the usual chemical tests, such as the blue color that develops in the iodide of starch, and the pretty reaction with a mixture of bichromate of potash and sulphuric acid. In this the free peroxide of hydrogen causes a beautiful blue color from perchromic acid developed, which

will dissolve in ether and float as a blue liquid on the surface. The greatest possible care is necessary in the preparation of this oxytuberculine, for if any appreciable quantity should escape oxidation, fatal tuberculine poisoning might result from the large quantities that must be administered. It should be carefully tested, first on animals and then on patients. This oxytuberculine, after it has been carefully prepared and tested, is injected hypodermically into any part of the body. I prefer the back, and inject the remedy well under the skin. The most scrupulous care must be taken. If the lymph should be in the least clouded or any other condition be present that would suggest infection, it should be sterilized by heat for at least 15 minutes. Ordinary syringes should not be used but such as are employed with antitoxine. I have made many thousand such injections without a single abscess, or even an induration of the skin. I show you here a patient into whose back many hundred injections have been made. You will find no sign of irritation or infiltration. In order that the method of using the remedy may be made clear I will now inject a syringe full. I begin with 5 c.c. injected daily and increased by 5 c.c. every three days until the dose 20 c.c. is reached, at which quantity I usually remain, but in many cases that has been far exceeded. I have injected as much as 100 c.c., over three ounces, or the equivalent of 5 c.c. of Koch's concentrated tuberculine, at one time into a patient without a rise of temperature, or any other immediate or subsequent unpleasant symptom.

The liquid causes no greater local disturbance than any indifferent fluid would produce. There is no reddening of the skin or other sign of localized inflammation. In a few minutes the fluid injected is absorbed, and the patient has no further inconvenience except sometimes a little smarting at the site of injection; there is no rise of temperature, nor any other unpleasant constitutional effect. Within a few days the cough and the expectoration diminish, and the most striking effect is the rapid improvement in the appearance of the patient. His eyes become bright and his color changes from the gray hue of tuberculosis to one more nearly resembling that of health. The appetite rapidly returns, and with it a feeling of vigor that is most pleasing to the patient and to the physician. That is especially evident in the very early cases in which there is little

or no fever. In cases in which only slight fever is present, the higher temperature soon diminishes, and in many instances becomes entirely normal. At the same time the infiltration of the lung gradually disappears, so that most careful examination fails to reveal any deviation from the normal whatsoever after the treatment is completed. The bacilli of tuberculosis in the sputum may rapidly diminish and finally disappear altogether, as I have found in a number of cases.

Every physician has seen cases of tuberculosis recover, but it has never before been my good fortune to witness such rapid changes as have taken place with several cases which have been examined by other physicians, both before and during the treatment. The patients that have recovered have thus far remained well. If any test of the method should be made by members of the profession, I would earnestly request that, provisionally, only early cases be treated in which there is no development of cavities in the lung, in whom fever is slight, and the constitutional effect such that a return to health may reasonably be expected.

One of the most striking demonstrations of the value of the remedy occurred in a local tuberculosis of the hand. A physician infected the dorsum of his right hand, and an ulceration developed which microscopic examination showed to be tubercular. It was treated in the usual manner without results, so that the surgeon was about to make an extensive excision, to be followed by skin-grafting. Instead thereof, local applications of the oxytuberculine were made, and very rapid healing took place, leaving behind the same kind of scar as would have resulted from a non-infected ulcer. The doctor has kindly consented to appear before you. You observe the scar upon his knuckle which shows no sign of the trouble which gave rise to it. The section prepared for microscopic examination by Dr. Rixford is open to your inspection. As a confirmation of this observation I show you here a dog that was vaccinated upon the back in a large number of places with a virulent pure culture of tuberculosis. After a short time numerous tubercular ulcers developed, in the pus of which the bacilli of tuberculosis were demonstrated; a section made by Dr. Rixford shows bacilli in the tissues. The dog was then chloroformed, and a piece of the skin with the tubercular ulcers was removed. This I have here preserved in formaline alcohol. The dog

was then treated with daily hypodermic injections of oxytuberculine. The ulcers rapidly healed, and you now see the animal with the scar resulting from the removal of part of the tubercular skin, but with no sign of the disease that was vaccinated into him. I will say that since the injections of oxytuberculine, the dog that was ailing, feeble and without desire for food, has become bright, strong and vigorous, and has developed a voracious appetite. You here see the photograph of the dog cured, and here an enlargement of the skin with the tubercular ulcers. (See Plate I.)

Of the cases that have been treated by me with the oxytuberculine those who came in the very early stage of the disease before cavities were present were rapidly cured. By cure I mean a complete cessation of cough and disappearance of all symptoms of disease on the part of the patient, together with the return of a normal condition of the lung as shown by physical examination. Above all do I demand that the bacilli of tuberculosis shall no longer be found in the sputum.

Cases that were moderately advanced have likewise rapidly improved, and some have entirely recovered, as you will see.

Of the very advanced cases many have shown marked improvement, and many whom I had declined to treat as being too far advanced but who pleaded so hard for the treatment that I could not refuse, have surprised me by the wonderful improvement they have shown.

Some in the last stages of the disease who presented themselves with high fever, cyanotic and gasping, have died. No treatment should be expected to reach such cases. Of course they throw a cloud upon the statistics, for they must be honestly reported with the most favorable cases. I shall therefore present to you all of the cases I have treated with oxytuberculine, but request you not to judge by the advanced cases for which I make no claim whatsoever. In order to systematize our observations I will divide the cases into four sets depending upon the stage of the disease. In the first stage we find infiltration of the lungs with more or less pallor, loss of weight, cough with sputum containing bacilli of tuberculosis. These may be absent at repeated examinations and yet be finally found.

In the second stage, we have extensive infiltrations of the lungs with hectic fever, emaciation, large quantity of sputum containing bacilli of tuberculosis, but no cavities.

In the third stage we have cavities but still a fair degree of vigor. There is no dyspnœa when the patient is quiet, but marked shortness of breath on exertion.

In the fourth stage we have large cavities with the usual signs of advanced consumption—the dyspnœa is very decided even when the patient is sitting or lying.

The distinctive features:

First stage—slight infiltration of the lungs.

Second stage—extensive infiltration of the lungs.

Third stage—cavities with dyspnœa on exertion, and none when at rest.

Fourth stage—cavities with dyspnœa when at rest.

Many of the cases here presented in person and in table have been seen by other physicians before and during the treatment. My colleagues have confirmed my observations, and I am certain that they will agree that I have not erred in making my reports too favorable. It has been my purpose to be as skeptical as possible, and I have striven to make the showing rather less favorable than too much so. I find that the cases that had been treated with oxytuberculine insufficiently oxidized, did not give the same results as those treated with the newer preparation, and have, therefore, separated them into a distinct table.

FOURTH STAGE—OLD METHOD.

No	Name.	Days Treated.	Bacilli.		Cured.	Much Improved.	Slightly Improved.	Unchanged.	Worse.	Died.
			Before.	After.						
1...	M. A.	123	Large.	Large.	.....	.....	1	.....	.....	.....
2...	E. B.	48	"	Not. Ex.	.....	.....	.....	.....	.....	1
3...	F. B.	77	"	"	.....	.....	.....	.....	.....	1
4...	H. C.	72	"	"	.....	.....	.....	.....	1	.....
5...	M. G.	106	"	"	.....	.....	.....	.....	1	.....
6...	G. A. H.	132	"	"	.....	.....	.....	.....	.....	1
7...	A. H.	48	"	"	.....	.....	1	.....	.....	.....
8...	G. H.	54	"	"	.....	.....	.....	1	.....	.....
9...	T. H.	30	"	"	.....	.....	.....	.....	1	.....
10...	J. Mc.	100	"	"	.....	.....	.....	.....	.....	1
11...	J. R.	102	"	"	.....	.....	.....	.....	1	.....
12...	G. St. D.	77	"	"	.....	.....	.....	.....	1	.....
13...	O. R.	120	"	"	.....	.....	.....	1	.....	.....
14...	J. H.	39	Mod.	"	.....	.....	.....	1	.....	.....
15...	A. V.	135	Large.	Few.	.....	.....	.....	.....	1	.....
16...	H. F.	90	"	Not. Ex.	.....	1	.....	.....	.....	.....

FOURTH STAGE—NEW METHOD.

No.	Name.	Days Treated.	Bacilli. Before.	Bacilli. After.	Cured.	Much Improved.	Slightly Improved.	Unchanged.	Worse.	Died.
1...	D. A. C.	172	Large.	Mod.	.....	.....	.....	1	.....	.....
2...	C. F.	165	"	"	.....	.....	1	.....	.....	.....
3...	T. J.	104	"	Not Ex.	.....	.....	.....	.....	1	.....
4...	G. A. K.	57	"	"	.....	.....	.....	.....	.....	1
5...	J. M.	481	"	None.	1	.....	.....	.....	.....	.....
6...	J. M.	365	"	Hrdly any	.....	1	.....	.....	.....	.....
7...	B. M.	363	"	Veryfew	.....	1	.....	.....	.....	.....
8...	W. R. P.	54	"	Large.	.....	.....	.....	1	.....	.....
9...	P. P.	235	"	Mod.	.....	1	.....	.....	.....	.....
10...	G. P. A.	199	"	"	.....	1	.....	.....	.....	.....
11...	D. H.	130	"	"	.....	1	.....	.....	.....	.....

THIRD STAGE.

1...	D. B.	26	Mod.	Not Ex.	.....	.....	.....	1	.....	.....
2...	S. D.	254	Large.	None.	1	.....	.....	.....	.....	.....
3...	E. E.	37	"	Not Ex.	.....	1	.....	.....	.....	.....
4...	A. G.	136	Mod.	Large.	.....	1	.....	.....	.....	.....
5...	F. J.	162	Large.	None.	.....	1	.....	.....	.....	.....
6...	M. L.	31	"	Large.	.....	.....	1	.....	.....	.....
7...	J. M.	141	"	Hrdly any	.....	1	.....	.....	.....	.....
8...	S. M.	365	"	Mod,	.....	1	.....	.....	.....	.....
9...	A. M.	30	"	Not Ex.	.....	1	.....	.....	.....	.....
10...	C. M.	22	Mod.	"	.....	.....	1	.....	.....	.....
11...	R. M.	237	Large.	Mod.	.....	1	.....	.....	.....	.....
12...	H. P.	285	"	None.	.....	1	.....	.....	.....	.....
13...	T. P.	33	"	Not Ex.	.....	.....	.....	1	.....	.....
14...	L. F.	40	Mod.	"	.....	.....	.....	1	.....	.....
15...	F. A. S.	198	"	Mod.	.....	1	.....	.....	.....	.....
16...	C. H. W.	42	Large.	Large.	.....	1	.....	.....	.....	.....
17...	M. W.	146	Mod.	Few.	.....	1	.....	.....	.....	.....
18...	T. H. W.	254	Large.	None.	1	.....	.....	.....	.....	.....
19...	T. M.	250	"	Mod.	.....	1	.....	.....	.....	.....
20...	F. D. R.	300	"	None.	.....	1	.....	.....	.....	.....
21...	W. H.	280	"	Mod.	.....	1	.....	.....	.....	.....
22...	M. W.	120	Small.	Small.	.....	1	.....	.....	.....	.....
23...	P. S.	40	Mod.	Mod.	.....	1	.....	.....	.....	.....
24...	J. D.	30	Large.	Large.	.....	1	.....	.....	.....	.....
25...	T. T.	80	"	Mod.	.....	1	.....	.....	.....	.....

SECOND STAGE.

No.	Name.	Days Treated	Bacilli.		Cured.	Much Improved.	Slightly Improved.	Unchanged.	Worse.	Died.
			Before.	After.						
1...	E. G.	258	Large.	None.	1	.....	.....	.....	.....	.....
2...	W. M.	75	Mod.	Not Ex.	.....	1	.....	.....	.....	.....
3...	N. R.	83	Large.	Hrdly any	.....	1	.....	.....	.....	.....
4...	F. C.	91	"	None.	.....	1	.....	.....	.....	.....
5...	Father S.	99	Mod.	"	1	.....	.....	.....	.....	.....
6...	V. C.[1]	100	None.	"	1	.....	.....	.....	.....	.....
7...	C. V.	90	Mod.	"	1	.....	.....	.....	.....	.....
8...	T. L.	180	Large.	"	.....	1	.....	.....	.....	.....
9...	R. W. R.[2]	36	None.	"	.....	1	.....	.....	.....	.....

FIRST STAGE.

1..	F. A. A.	134	Mod.	None.	1	.....	.....	.....	.....	.....
2...	M. L.	16	None.	"	1	.....	.....	.....	.....	.....
3...	W. Q.	395	"	"	1	.....	.....	.....	.....	.....
4...	R. W. R.	106	"	"	1	.....	.....	.....	.....	.....

GENERAL SUMMARY.

Stage.	Total No. Treated.	Cured.	Much Improved.	Slightly Improved.	Unchanged.	Worse.	Died.
Fourth Stage—Old Method	16	.....	1	2	3	6	4
Fourth Stage—New Method	11	1	5	1	2	1	1
Third Stage	25	2	18	2	3	.....	.....
Second Stage	9	4	5	.....	.....	.....	.....
First Stage	4	4	.....	.....	.....	.....	.....
	65	11	29	5	8	7	5

Clinical observation having thus shown the very marked effect of oxytuberculine, it remains for us to establish in what manner is this cure effected. There are two modes in which the body may rid itself of an invading micro-organism. The one is by the enfeeblement of the germ, and the other is by the invigoration of the body so that it becomes sufficiently potent to expel the invader. We know that we are all constantly taking the bacillus of tuberculosis into our bodies. It has been

[1] Sputum (through oversight) not examined until the patient had been treated one month.

[2] Bacilli found by former physician who sent the patient to me.

shown by Loomis, at post-mortem examinations of healthy individuals who have died of accident, that many have the bacillus of tuberculosis stored up in the bronchial glands out of harm's way, but alive and able to infect guinea pigs when injected into them. Yet we cannot call such individuals tubercular. Again, we constantly observe that tuberculosis develops when the patient becomes physically depressed, when the vital forces are at low ebb. On the other hand, innumerable cases of consumption recover under the influence of favorable hygienic conditions. The antitoxines of the infectious diseases probably act in a somewhat similar manner, for experiment has proved that they neutralize the pernicious toxines which are formed by the germs and which enfeeble the body by their poisonous influence.

Upon the germs themselves they have little influence, for we know that the pathogenic organisms flourish in the very serum which is used to antagonize their effect upon the body. How is it with oxytuberculine? It will be my pleasant privilege to prove to you this evening that oxytuberculine directly prevents the growth of the bacillus of tuberculosis, that its action is specific upon that germ, and not due to a general antiseptic effect. If we take veal bouillon containing 4 per cent glycerine, 1 per cent peptone and one-half per cent salt, and add to every 1000 c.c. thereof, when neutralized to litmus, 3 c.c. of a normal solution of carbonate of soda, we will find that the bacillus tuberculosis will grow vigorously upon it. If we mix this veal bouillon with equal parts of tuberculine made similarly alkaline the germ will flourish just the same. But if we use oxytuberculine made from the same tuberculine rendered alkaline to the same degree the bacillus of tuberculosis will not grow. In other words, the oxytuberculine inhibits in the culture tube the growth of the germ of tuberculosis just as it cures the consumption in the patient. Not only can this be proved by the simple culture experiment, but the strength of the oxytuberculine can be most accurately gauged by the same process. If to our standard alkaline glycerine veal bouillon we add oxytuberculine in varying proportions, it will be a simple matter to find the weakest dilution of the oxytuberculine in which the growth of the bacillus will be inhibited, and thus may it be standardized. In this photograph you see represented the growth of tuberculosis bacillus on mixtures of standard veal

bouillon with varying portions of oxytuberculine made three-tenths per cent normal alkaline and water, also made three-tenths per cent normal alkaline. You see a gradual diminution of the development as the addition of oxytuberculine becomes stronger. When the mixture contains 7 parts of oxytuberculine in 20, growth ceases, and beyond this strength no growth occurs. That is to say, a dilution of this oxytuberculine to 30 per cent prevents the development of the germ. We may therefore call this preparation 300 per cent strong. (See Plate II.)

In a similar manner any oxytuberculine may be standardized so that when we use it we may know accurately how potent is the remedy that we are employing. Such a method of estimating the strength of a preparation is infinitely superior to that of judging it from its effect upon more or less resistant animals.

From the very beginning of the experiments it has been my purpose to find some means of knowing how long I should continue the oxidation in order that all of the tuberculine should be changed to oxytuberculine and none of the latter destroyed. There was no chemical test known, and all my efforts to find one were in vain. I was, therefore, compelled to make use of the reaction of tubercular guinea pigs to find the point when no effective tuberculine could be found. It is clear that a certain amount of the tuberculine might be present, but neutralized in its effects by the oxytuberculine. Under such circumstances we would get no deleterious tuberculine influence, but still not the best possible oxytuberculine action. In the manufacture of the oxytuberculine I had gradually come to lengthen the time during which I heated the tuberculine with the peroxide of hydrogen, and had finally decided upon the method of sterilizing for four days. Oxytuberculine so prepared gave excellent results and no reactions until I happened to use large doses, 40 c.c., with a highly sensitive hospital patient named Stewart. A slight rise of temperature occurred that made me feel that all of the tuberculine had not been converted. About this time I had discovered the inhibitory influence of the oxytuberculine, and I immediately concluded that this influence would teach me what was the best length of time to

continue the oxidation. I reasoned that, if my theory were right, as I continued the oxidation, this inhibitory power must gradually increase until the maximum is reached, and as the oxytuberculine produced is gradually destroyed by further oxidation, from this point on there must be a gradual decline of this inhibitory power. Such, indeed, was the result obtained. I sterilized tuberculine with peroxide of hydrogen for 176 hours, adding the peroxide every 12 hours, and removing portions of the lymph for comparison at 96, 120, 144, and 156 hours. The final oxytuberculine, that sterilized 176 hours, contained but 53 per cent of the quantity that was present in that sterilized only 96 hours, and in order to make a fair comparison after free peroxide in all the preparations was removed by rendering them alkaline and heating, all were diluted to the same proportion with distilled water, the quantity added depending upon the degree to which it had been diluted in the process of preparation by addition of peroxide of hydrogen, which, of course, had become changed to water. All of the preparations were then neutralized, and three-tenths per cent normal carbonate of soda was added. Each of the oxytuberculines was mixed with an equal quantity of standard veal bouillon and inoculated with a pure culture of the bacillus tuberculosis. As a control, standard veal bouillon was mixed with an equal quantity of water, to which three-tenths per cent normal carbonate of soda was added and was likewise inoculated with the same germ. The relative growth is shown by the photograph of the bottles in which they have developed. (See Plate III.)

They show rapid growth in the veal bouillon, less in the 96 hour oxytuberculine, and hardly any in the 120 hour oxytuberculine, which you will remember had been diluted with water and veal bouillon to only 26½ per cent. In the 144 hour oxytuberculine growth increased, and was greater in the 156 hour preparation, and in that sterilized in the 176 hour was almost as great as in the veal bouillon. This simple little experiment not only confirmed our previous culture tests, but likewise taught that at least 120 hours and less than 144 hours are necessary to get best results. In point of fact, as soon as I began to use oxytuberculine so prepared upon my patients, immediate and striking results occurred such as I had not wit-

nessed before. I shall now narrow the range still more by tests of the oxytuberculines heated for different periods between 120 and 144 hours. I have done this in part with another sample of oxytuberculine that was sterilized 144 hours and a portion removed after 134 hours sterilization. These were made three-tenths per cent normal alkaline, and each mixed with equal quantities of standard veal boullion. They were inoculated with the tuberculosis at the same time as was veal boullion. Three cultures of veal boullion and 4 each of 134 and 144 hours oxytuberculine were made. All of the veal boullion and all of the 144-hour oxytuberculine flasks showed vigorous growth, and none of the 134-hour tuberculine flasks, as you can see from this photograph. (See Plate IV.)

Provisional experiments made with cultures of staphylococcus, micrococcus ureæ, bacillus typhosus, and bacillus diphtheriæ have given results analogous to those obtained with the bacillus tuberculosis. Cultures of these germs were sterilized and filtered in the same manner and were oxidized similarly with the peroxide of hydrogen for various periods and then treated in the same manner. They were likewise mixed with veal boullion and inoculated with the respective germs, as was likewise a control with veal boullion. In all of them a complete suppression of the growth of the micro-organisms occurred, but the length of time of oxidation that was necessary to produce this result differed with different germs. The presence of the inhibitory action of the oxytoxine upon growth of the germ in 4 cases in addition to that observed with tuberculosis, proves the universality of the law, and permits us to reason from analogy that not only will all of these diseases yield to oxytoxic treatment, but that this must be true of every disease whose germ we can cultivate.

I will now call your attention to these tables, which show the effect of the oxytoxines of the various germs. As my attention had been directed to the faint possibility that the inhibitory influence might be due to the reaction of peroxide of hydrogen on veal boullion, I treated that liquid with the oxidizer in the same manner as the cultures, sterilizing for 130 hours, and found that it had no effect whatsoever in any case.

MICROCOCCUS UREÆ.

Hours of Oxidation.	Hours of Growth. 24	30	43	70
43	?	Growth	Growth	Growth
65	No	No	No	No
90	No	No	No	No
125	No	No	No	No
130	No	No	No	No
Veal Bouillon.....	Growth	Growth	Growth	Growth

TYPHOID.

43	Growth	Growth	Growth	Growth
65	Growth	Growth	Growth	Growth
90	Growth	Growth	Growth	Growth
125	Growth	Growth	Growth	Growth
130	No	No	No	No
Veal Bouillon.....	Growth	Growth	Growth	Growth

DIPHTHERIA.

43	Growth	Growth	Growth	Growth
65	No	No	No	No
90	No	No	No	No
125	No	No	No	Slight
130	Growth	Growth	Growth	Growth
Veal Bouillon.....	Growth	Growth	Growth	Growth

STAPHYLOCOCCUS.

43	Growth	Growth	Growth	Growth
65	Growth	Growth	Growth	Growth
90	Growth	Growth	Growth	Growth
125	Growth	Growth	Growth	Growth
130	No	No	No	No
Veal Bouillon.....	Growth	Growth	Growth	Growth

All of these tests show conclusively that the oxytuberculine inhibits the growth of the bacillus tuberculosis. That this is a specific effect and not due to a general antiseptic action is proved by the facility with which other germs develop in the fluid. I have here a bottle of oxytuberculine in which air-born germs have grown vigorously. The readiness with which this occurs has made it necessary to add boric acid to prevent the decomposition of the lymph.

From all of the statements made I believe I have proved beyond reasonable doubt that consumption may be cured with oxytuberculine, if administered before the later stages of the disease and that the cure is effected by a direct action upon the causal germ.

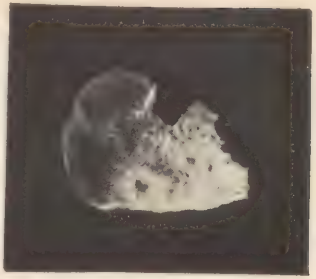

PLATE I.

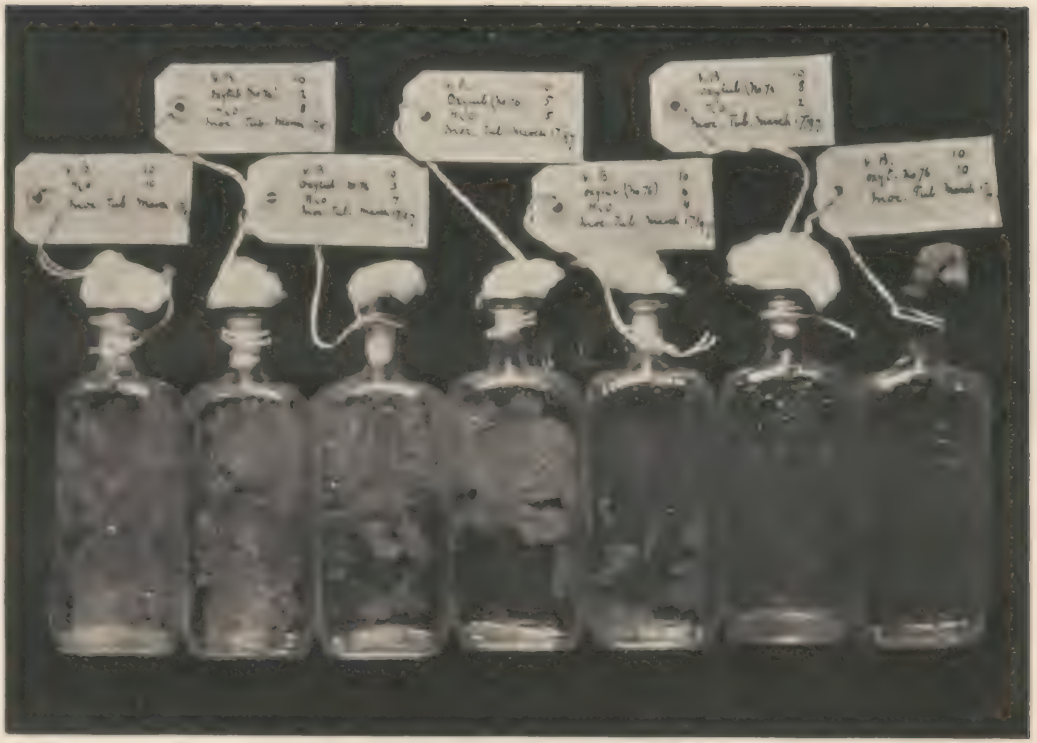

PLATE II.

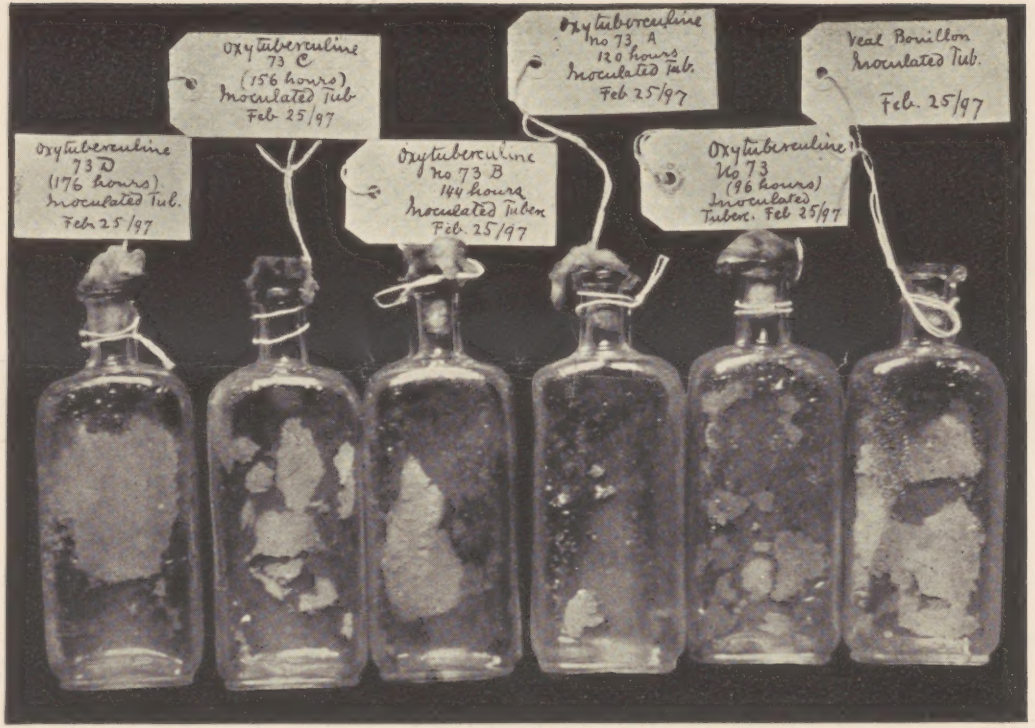
Oxytuberculine
73 C
(156 hours)
Inoculated Tub
Feb 25/97
Oxytuberculine
73 D
(176 hours)
Inoculated Tub.
Feb 25/97
Oxytuberculine
No 73 B
144 hours
Inoculated Tuben
Feb. 25/97
Oxytuberculine
No 73 A
120 hours
Inoculated Tub.
Feb 25/97
Oxytuberculine
No 73
(96 hours)
Inoculated
Tuber. Feb 25/97
Veal Bouillon
Inoculated Tub.
Feb. 25/97

PLATE III.


V. B. 10
H_2O 10
Inoc. Tub. March 4/97
V. B. 10
Oxyt. 79A (134 hrs) 10
Inoc. Tub. March 4/97
V. B. 10
Oxyt. 79A (144 hrs) 10
Inoc. Tub. March 4/97

PLATE IV.

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